REMARKS

Claims 1-26 and 31-34 are pending in this application. Claims 17-26 and 31-34 are withdrawn. Claims 1-16 have been rejected. Claims 7, 28-30 have been canceled. Claims 35-36 have been added. Support for claims 35 and 36 may be found in claim 2 as originally filed and on page 2, last paragraph to page 3, first paragraph. Claims 2, 6, 10, 13, 15, 16 have been amended to clarify the invention. Support for the amendment for claim 6 may be found on page 3, second paragraph. It is believed no new matter has been added.

Election/Restrction

The Examiner made the restriction requirement final, arguing that the combination of the references (Chakrabarti et al., *Biochem. Biophys. Res. Comm.*, 264:871-877 (1999) and Dong et al., *Blood* 99(8):2637-2646 (2002)) together provide a correlative relation between TEL/Etv6 signaling and Stat3 regulation of cell proliferation, suggesting that the signaling elements are directly interactive. Without acquiescing as to the accuracy of the Examiner's argument, Applicants confirm the election, with traverse, of Group I, claims 1-16, drawn to a method for identifying an agent that modulates Stat3 through modulating TEL/Etv6 activity.

Specification

The Examiner objected to the disclosure on related priority documents because it does not include the relationship to PCT/EP03/12295 and GB 0225799.6. Applicants have amended the first paragraph of the specification to include all priority documents claimed on May 2, 2005, dates they were filed and their relationships to the current application.

Claim Objections

Claim 10 has been objected to for reciting "the test compound" wherein claim 1, to which claim 10 depends, recites "the compound". Applicants have amended claim 10, as suggested by the Examiner, to recite "said compound" to avoid any inconsistency.

Similarly, claim 16 has been amended to clarify the claim by including the phrase "in a reporter gene construct" as suggested by the Examiner.

The Examiner had suggested that Applicants check the specification for the proper use of a trademark, e.g., be accompanied by the generic terminology. Applicants note the Examiner's suggestion and will amend the specification, prior to issuance, to properly identify the trademarks.

35 U.S.C. § 112, Second Paragraph

The Examiner rejected claims 1-9 and 11-16 under 35 U.S.C. § 112, second paragraph. In particular, the Examiner found that claims 1-5 are incomplete for omitting essential steps of "identifying the modulating effect of the test compound selected in step iii) of claim 1 on Stat3-dependent cell proliferation." Applicants respectfully disagree. The step iii) of claim 1 requires determining a compound-induced modulation in the TEL/Etv6 activity relative to when said compound is absent. This step, therefore, inherently encompasses the step of identifying the modulating effect of the test compound on Stat3-dependent cell proliferation. As such, the essential step noted by the Examiner has not been omitted.

Similarly, the Examiner rejected claims 6-9, 11-3, 15 and 16 under Section 112, second paragraph for being incomplete, allegedly omitting essential steps such as "[determining] a) the nexus between the binding agent, TEL/Etv6 and Stat3 in claim 6, b) the step of identifying the modulcating effect of the test compound selected in step ii) of claim 6 on Stat3-dependent cell proliferation and c) the nexus for reporter gene expression upon contact between TEL/Etv6 and the binding partner on to Stat3-dependent cell proliferation in claim 16." *Office Action*, 9/3/08, page 6. Similar to the arguments made above, step (ii) of claim 6 requires determining whether the presence of a test compound modulates the interaction between said TEL/Etv6 polypeptaide and the binding partner relative to when the test compound is absent. Therefore, the step of identifying the modulating effect of the test compound suggested by the Examiner is inherent in step (ii) of claim 1. In addition, it is not necessary to determine the "nexus between the binding agent, TEL/Etv6 and Stat3" every time a skilled artisan performs the claimed method of identifying an agent effective in modulating Stat3-dependent cell proliferation. The

Specification discloses and provides a reasonable basis supporting that "TEL/Etv6 is an inhibitor of Stat3 activity and modulation of TEL/Etv6 allows regulation of the Stat3 signaling pathway (see Example 6). Accordingly, the present invention provides a method of identifying an agent effective in reducing STAT3-dependent cell proliferation, based on the modulation of TEL/Etv6 levels or TEL/Etv6 activity". *Specification*, pages 4-5. As such, the specification established the nexus between TEL/Etv6, Stat3 and the test compound. Performing this step every time a skilled artisan performs the claimed methods, while not excluded, is not required.

The Examiner argued that claim 2 is indefinite because the language "said agent is effective in enhancing cytokine-induced inhibition of cell proliferation" is broader than generic claim 1. The Examiner further questions the correlation between Stat3-deepndent and cytokine-dependent cell proliferation. Without acquiescing to the accuracy of the Examiner's statement, Applicants amended the claim to remove of language to which the Examiner objected.

The Examiner rejected claim 7, arguing that claim 7, on the one hand, requires that the variant or fragment of TEL/Etv6 bind Stat3 while claim 14 only describes the physical association between TEL/Etv6 and Stat3. To expedite allowance of the claims, Applicants have canceled claim 7.

The Examiner rejected claim 13 for reciting "the substance" which lacks antecedent basis. Applicants therefore amended the claim to refer to "the test compound" to overcome the Examiner's rejection. The Examiner further rejected claim 13 for reciting "confirming the substance inhibits cell proliferation of a cytokine-sensitive cancer" because such recitation is broader than the generic claim 6. Applicants respectfully disagree. Claim 6 provides for a method of identifying an agent effective in modulating stat3-dependent cell proliferation. It, therefore, provides a starting point for narrowing down an unlimited number of possible agents to a finite number of possible agents effective for modulating stat3-dependent cell proliferation. Claim 13 further limits claim 6 by requiring the step of confirming that the substance in fact inhibits cell proliferation of a cytokine-sensitive cancer. Contrary to the Examiner's contention that claim 13 broadens claim 6, claim 13 in fact further limits claim 6.

The Examiner rejected claim 15[1] for the recitation of "identifying substances which inhibit said interaction in said cell" for failing to describe the relationship between the identified substance and the test compounds in the preceding step. Applicants have amended claim 15 to change "substance" to "test compound" to clarify the claim.

Based on the current amendments and for reasons stated herewith, Applicants earnestly request withdrawal of the rejections under Section 112, Second Paragraph.

Biological Deposit

The Examiner rejected claims 15 and 16 under 35 U.S.C. § 112, first paragraph for lack of enablement, suggesting deposit of biological samples to enable the invention. The Examiner admitted that the specification teaches constructs for TEL mutants that are transfected into Stat3-ER-A375 cells and HEK 293 cells, but argued that it is unclear if cell or cell line expressing TEL/Etv6 variant or a fragment thereof is known, publicly available or can be producibly isolated without undue experimentation. Applicants respectfully traverse. MPEP 2402 does not require deposits of biological material in every instance, but only "[w]here the invention involves a biological material and words alone cannot sufficiently describe how to make and use the invention in a reproducible manner". *Id.* The case law is also clear that "[a] patent need not teach, and preferably omits, what is well known in the art." MPEP 2164.01, citing *In re Buchner*, 929 F.2d 660, 661, 18 USPQ2d 1331, 1332 (Fed. Cir. 1991); *Hybritech, Inc. v. Monoclonal Antibodies, Inc.*, 802 F.2d 1367, 1384, 231 USPQ 81, 94 (Fed. Cir. 1986), *cert. denied*, 480 U.S. 947 (1987); and *Lindemann Maschinenfabrik GMBH v. American Hoist & Derrick Co.*, 730 F.2d 1452, 1463, 221 USPQ 481, 489 (Fed. Cir. 1984).

Here, contrary to the Examiner's contention, TEL/Etv6 is known in the art and cells expressing wild type TEL/Etv6 are also known at the time of the filing of the current

[1] The Examiner specifically rejected claim 16 and referred to element (ii) "identifying substances which inhibit said interaction in said cell", but this element is recited in claim 15 and not explicitly recited in claim 16. While dependent claim 16 incorporates all of the limitation of claim 15, to which claim 16 depends, claim 16 does not explicitly recite that language. It is assumed that the Examiner meant to reject claim 15. Should the Applicants be incorrect, Applicants invite the Examiner to clarify this rejection.

application. *See* Fenwick et al., *Molecular and Cellular Biology* (2000) 20(16):5828 (previously cited). In addition, the specification discloses that:

> [t]he nucleic acid [of the invention] will typically be provided in a vector allowing replication in one or more selected host cells, as is well known for a variety of bacteria, yeast, and mammalian cells. For example, various viral origins (SV40, polyoma, adenovirus, VSV or BPV) are useful for cloning vectors in mammalian cells. The vector may, for example, be in the form of a plasmid, cosmid, viral particle, phage, or any other suitable vector or construct which can be taken up by a cell and used to express the sequence of interest or reporter gene. The constructs may be expressed transiently or as stable episomes, or integrated into the genome of the host cell . . .
>
> the methods of the invention may further include introducing the nucleic acid into a host cell . . . Host cells transfected of transformed with expression or cloning vectors described herein may be cultured in conventional nutrient media. The culture conditions, such as media, temperature, pH and the like, can be selected by the skilled artisan without undue experimentation . . .

Specification, page 10-11. As TEL/Etv6 gene is known in the art and cell transfection or transformation for expression or cloning of various vectors is commonly done and well within the general knowledge of a skilled artisan, the disclosure of the specification provides sufficient guidance to produce cells expressing TEL/Etv6 as disclosed in claim 15 and 16. To produce cells expressing variants or fragments of TEL/Etv6, page 5, third paragraph of the specification provides guidance and definition as to what the variant or fragment entail. In addition, Example 8 of the specification also teaches and identifies regions of TEL which are required for Stat3 transcriptional activity (e.g., TEL delta 333-452). Given such information, producing cells expressing TEL/Etv6 variants or fragments thereof would not require undue experimentation. As such, the specification sufficiently describes to those skilled in the art how to cells expressing TEL/Etv6, a variant or fragment thereof to practice the invention as claimed in claims 15 and 16 and

therefore does not necessitate deposit of biological material. Withdrawal of the rejections under Section 112, first paragraph is earnestly requested.

35 U.S.C. § 112, First Paragraph - Enablement

The Examiner rejected claims 1-16 under 35 U.S.C. § 112, first paragraph for lack of enablement. The Examiner admitted that the specification is "enabling for screening agents that modulate TEL-mediated repression of Stat3 transcriptional activity from a Stat3-ER reporter construct and/or that modulate TEL binding to Stat3 in cytokine-responsive tumor cell lines', but argued that the specification "does not reasonably provide enablement for correlating the modulation of any TEL activity or the binding of TEL to any binding partner in the presence of any test agent, to where the agent modulates Stat3-dependent cell proliferation in any cell or cell line". *Office Action*, 9/3/08, p. 10. Instead of accepting the inventors' conclusion based on experimental data that TEL is a transcriptional repressor of Stat3 transcriptional activity by interacting with Stat3 directly and recruiting HDAC to the Stat3 transcriptional complex", the Examiner argued that it would not be predictable that "the binding of TEL alone to Stat3 would inhibit Stat3 transcriptional activity". While admitting that Applicants have demonstrated that TEL repressor activity for Stat3-mediated transcriptional activity could be blocked by Trichostatin A, the Examiner, nevertheless argued that "it is not predictable that . . . any test compound could inhibit [the] interaction [between TEL and Stat3] to modulate Stat3 transcriptional activity measured by cell proliferation ". Consequently, the Examiner concluded that "the specification is not enabling for screening drugs where modulation or alteration of any TEL activity is correlative with modulating Stat3-dependent cell proliferation." The Examiner is essentially challenging the asserted utility of the invention.

Applicants respectfully disagree. MPEP 2164.04 provides that "a specification disclosure which contains a teaching of the manner and process of making and using an invention in terms which correspond in scope to those used in describing and defining the subject matter sought to be patented must be taken as being in compliance with the enablement requirement of 35 U.S.C. 112, first paragraph, unless there is a reason to

doubt the objective truth of the statements contained therein which must be relied on for enabling support." *Id.* The Federal Circuit in *In re Brana*, 51 F.3d 1560 (Fed. Cir. 1995) stated that "the initial burden of proving non-enablement is on the patent office. Only after the PTO provides evidence showing that one of ordinary skill in the art would reasonably doubt the asserted utility does the burden shift to the applicant to provide rebuttal evidence sufficient to convince such a person of the invention's asserted utility." *Id.*, 51 F.3d at 1566. Likewise, the Court in *In re Marzocchi*, 439 F.2d 220 (C.C.P.A. 1971) stated that "it is incumbent upon the Patent Office, whenever a rejection on this basis is made, to explain why it doubts the truth or accuracy of any statement in a supporting disclosure and to back up assertions of its own with acceptable evidence or reasoning which is inconsistent with the contested statement. Otherwise, there would be no need for the applicant to go to the trouble and expense of supporting his presumptively accurate disclosure." *Id.*, 439 F.2d at 224 (emphasis added).

Here, the Examiner merely argued, without providing any scientific support or reasonable basis as to why it would not be predictable that the binding of TEL to Stat3 would inhibit Stat3 transcriptional activity, or "that any test compound could inhibit this interaction to modulate Stat3 transcriptional activity measured by cell proliferation" when the specification provides a series of examples demonstrating a nexus between inhibiting TEL expression and Stat3 activity. For instance, Example 3 of the specification shows that 4-hydroxytamoxifen (4-HT), a ligand for estrogen-receptor ligand binding domain which activates Stat3-dependent transcriptional activity, is able to reduce A375-Stat3-ER cell number by 40%. Example 6 of the specification further shows that in the presence of TEL siRNA, Stat3-mediated inhibition of A375 cell proliferation significantly increased (from about 28% to about 40%). In addition, 4-HT- or oncostatin M (OSM – a potent activator of Stat3 transcriptional activity)-induced Stat3-dependent transcription luciferase significantly increases when TEL expression was reduced by siRNA. Example 6, therefore, shows that TEL is acting as a Stat3-induced negative regulator of Stat3 activity. The specification further demonstrates in Example 7 that trichostatin A, a general histone deacetylase (HDAC), prevents repression of Stat3 activity by TEL in 4-HT stimulated cells, but has no effects on Stat3-mediated transcriptional activity in

pcDNA3.1-transfected cells, indicating that TEL's inhibitory effect on Stat3-mediated transcription is dependent on the recruitment of HDAC. Example 9 shows that, in a Stat3 immunoprecipitation, the level of TEL associating with Stat3 increases in OSM-treated nuclear extracts compared to control. This example also shows that Stat3 is present in a TEL-containing complex pulled down through an immobilized GGAA-containing oligonucleotide that binds TEL, suggesting that TEL interacts directly with Stat3 and recruits HDAC to the Stat3 transcriptional complex when repressing Stat3 transcriptional activity. As such, the specification provides a reasonable basis supporting the role of TEL/Etv6 in Stat3-dependent cell proliferation. Applicants respectfully submit that the Examiner has not met her burden of providing evidence and/or reasoning as to why one skilled in the art would reasonably doubt that TEL represses Stat3 transcriptional activity be interacting directly with Stat3 and recruiting HDAC to the Stat3 transcriptional complex.

With respect to the Examiner's argument relating to the universe of binding partner(s) encompassed by the claim, Applicants have amended claim 6 to change from "a binding partner" to "Stat3, a variant or fragment thereof". In light of the amendments to the claim and the comments provided herewith, withdrawal of the rejections under 35 U.S.C. 112, first paragraph is respectfully requested.

35 U.S.C. § 103, First Paragraph - Enablement

The Examiner rejected claims 1-16 under 35 U.S.C. § 103(a) in view of Chakrabarti et al., *Biochem. Biophys. Res. Comm.* (1999) 264:871-877, Dong et al., *Blood* (2002) 99(8):2637-2646 and Kortylewski et al., *Oncogene* (1999) 18:3742-3753. The Examiner argued the following: that (1) "Chakrabarti discloses that TEL is a transcriptional repressor which involves the recruitment of a repressor complex including SMART, Sin3A, NcoR, which is further mediated through histone deacetylases (HDACs)"; (2) Dong et al. discloses that "SMRT and CoR are recruited with Stat5 for regulating Stat3 activity." (3) Kortylewski teaches that members of IL-6 family of cytokine, e.g., IL-6, OSM, LIF and CNF, have been shown to inhibit proliferation of some cancer (e.g., leukemia, melanoma, prostate and breast cancer cells), which

inhibition is mediated by Stat3 and that in some context, Stat3 has anti-proliferative and anti-oncogenic effects." *Office Action*, 9/3/08, p.19-20. Based on the findings above, the Examiner argued that "because it was known that TEL was a repressor of many transcriptional activity for many genes and regulation of Stat3 activity was possible because of the shared co-factors between TEL and Stat5, one skilled in the art would have been motivated to have formulated a method assay for screening drugs that modulated the activity of TEL (or its binding with SMRT or CoR) in order to modulate the activity of Stat3 because of the motivation provided in the references to identify mechanisms for regulating cytokine-mediated cell proliferation which affect Stat3."

Applicants respectfully disagree. None of the prior art cited by the Examiner suggests that TEL/Etv3 may be a regulator of Stat3 activity. The fact that Charkrabarti and Dong et al. in combination teach that TEL/Etv6 and Stat3 share common co-repressors such as SMRT and COR does not by itself render obvious the relationship between TEL/Etv6 and Stat3. There are other factor(s) that are involved in Stat3-dependent cell proliferation, namely HDAC, which Dong et al. does not disclose. In addition, the role of Stat3 in cell proliferation is unclear as the prior art has shown Stat3 to be an oncogene in some instances while also being a mediator of cytokine-induced inhibition of tumor cell proliferation in other instances. As such, one skilled in the art would not have formulated a screening method that modulates TEL/Etv6 activity or the interaction between TEL/Etv6 and Stat3 and have an expectation of success in Stat3-dependent cell proliferation. The current inventors, on the other hand, demonstrated the effects of: (i) Stat3 activation on the different phases of cell cycle and cell proliferation (See Example 3); (ii) TEL siRNA on Stat3-dependent transcriptional activity and the over-expression of TEL on Stat3 activity in Stat3ER A375 cells in response to induction by 4-hydroxytamoxefen and OSM (See Example 6); (iii) an HDAC inhibitor, namely trichostatin A, on the repression of Stat3 activity (See Example 7); (iv) TEL mutants on the repression of Stat3 transcriptional activity; and (v) OSM on the interaction between TEL and Stat3 in nuclear extract. Only through meticulous experimentations of the current inventors was the target of TEL/Etv6 and its effect on Stat3 activity and Stat3-dependent cell proliferation elucidated. The claimed inventions would only be obvious

based on an improper hind sight reconstruction of the inventions in view of Applicants' disclosure in the specification. It is respectfully submitted that the references cited do no render the claims of current invention obvious. Applicants respectfully request the withdrawal of the rejections under 35 U.S.C. 103(a).

CONCLUSION

Applicants respectfully submit that the claims are in conditional for allowance. The Examiner is invited to telephone Applicant's attorney at anytime should there be any questions.

As this response is filed within three months of the mailing date of the office action dated September 3, 2008, it is believed no fees are required. If this is not correct, however, please charge any additional fees, or credit any overpayment, to Deposit Account No. 50-4255.

Respectfully submitted,

Date Dec 2, 2008

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